

REMARKS

Claims 9-14, 41-49, 88-89, 91-92, and 142-174 were pending in the application. New claims 175-196 have been added. Claims 88, 91, 92, 144 have been amended to correct for dependencies and formalities. Thus, upon entry of this Amendment, claims 9-14, 41-49, 88-89, 91-92, and 142-196 are pending in the application. For the convenience of the Examiner, Applicants provide a readable copy of the claims in Appendix A, attached herewith.

Support for the amendment to claims 89 and 174 can be found throughout the specification, including at least at page 91, lines 29-31. Support for new claims 175 and 182 can be found throughout the specification, including at least at page 91, lines 26-31, at page 92, lines 15-16, at page 93, lines 24-25, and at page 94, lines 11-12. Support for new claims 176 and 177 can be found throughout the specification, including at least at page 92, line 16 to page 93, line 23. Support for new claim 178 can be found at least at page 93, line 24 to page 94, line 10 of the specification. Support for new claim 179 can be found in the specification, including at least at page 94, lines 11-26. Support for new claims 180 and 181 can be found throughout the specification, including at least at page 94, lined 27 to page 95, line 16. Support for new claims 183 and 184 can be found throughout the specification, including at least at Table 2 (Appendix A) and at page 134, lines 10-14 and Table 8. Support for new claim 185 can be found in the claims as originally filed. Support for new claims 186-190 can be found in the claims as originally filed and in the specification at Table 2 (Appendix A) and at page 39, line 15 to page 40, line 11. Support for new claims 191-193 can be found in the specification at Table 2 (Appendix A) and at page 117, line 32 to page 126, line 11. Support for new claims 194-196 can be found in the specification at Table 2 (Appendix A) and at page 124, lines 17-36.

No new matter has been added. Applicants request that the amendments to the specification and claims be entered. The foregoing claim amendments and cancellation should in no way be construed as an acquiescence to any of the Examiner's rejections and were made solely to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Interview Summary

Applicants acknowledge and thank the Examiner and her supervisor, Bonnie Eyler, for the personal interview with Applicants' attorney on October 17, 2003. The presented claims were discussed and agreed upon for submission during the personal interview.

Rejection of Claims 2-14, 63, 74, 76-83, 87-93 Under 35 U.S.C. § 112, First Paragraph*I Rejection of Claims 2-14, 63, 74, 76-83, 87-93 Under 35 U.S.C. § 112, First Paragraph*

The Examiner has rejected claims 2-14, 63, 74, 76-83, 87-93 under 35 U.S.C. 112, first paragraph, stating that the specification "does not enable any person skilled in the art to which it pertains...to make or use the invention commensurate with the scope of the claims." In the September 23, 2003 response, Applicants presented support from the instant specification describing the developmental process of obtaining antibodies with high affinity for IL-12 by outlining the evolution of antibody J695 from Joe 9, the originally identified antibody. In addition to the response filed on September 23, 2003, Applicants submit the following supplemental comments in support of Applicants' submission that the teachings of the specification and fully enable one of ordinary skill in the art to make and use the claimed antibody.

The specification describes the progression of identifying a human antibody with high affinity for IL-12 by teaching the process of screening/mutagenizing antibodies in order to identify antibodies with preferred characteristics, *i.e.*, high affinity for IL-12. The specification teaches first screening and identifying antibodies which possess the preferred characteristics, mutagenizing said antibodies to further improve the desired characteristics, and finally repeating the screening/mutagenizing process until antibodies with the desired characteristics are obtained. Based on the screening/mutagenizing process taught in the specification, Applicants identified numerous antibodies with the

desired high affinity properties, *e.g.*, k_{off} rate constant of $1 \times 10^{-3} \text{ s}^{-1}$ or less, as described in the response of September 23, 2003 and in further detail below:

In the initial antibody screen described in the specification, Applicants identified human antibodies which bind IL-12, including Joe 9 (see page 37, lines 10-24 and Example 1 of specification). The initial screen included screening human light and heavy chain antibody cDNA libraries with hIL-12 using phage display (see page 37, lines 12-19 and page 116, lines 6-11 of specification). Antibody Joe 9 was selected from the anti-IL-12 antibodies identified in the screen because it was specific to IL-12, was the closest to germline sequences COS-3, and was effective at inhibiting IL-12 activity in neutralization assays, including the IL-12 receptor binding assay (RBA assay) and the IL-12 induced proliferation of PHA stimulated human blast cells (PHA assay) (see specification at page 117, lines 5-15 of specification).

Following identification, Joe 9 was subject to affinity maturation, wherein the CDR3 of Joe 9 was randomly mutagenized to improve the binding affinity. Variants of the light and heavy chains of Joe 9 were created by site-specific PCR mutagenesis using degenerate oligonucleotides specific for either the heavy or light chain CDR3 (see page 117, lines 16-30 of specification). The resulting variant clones were screened and analyzed by Biocore analysis to determine which clones had improved affinity properties compared to the parent antibody, Joe 9 (page 118, lines 16-28 of specification). Clones with improved k_{off} rates were then analyzed for their neutralization properties using the RBA, PHA, and/or the inhibition of interferon gamma production (IFN gamma) assays (see page 118, lines 28-37 of specification). Clones 70-1 and 78-34 were selected based on their affinity and neutralization characteristics. As shown in Table 2 (Appendix A), clone 70-1 comprises the Joe 9 light chain CDR3 and a unique heavy chain CDR3 and clone 78-34 comprises a unique light chain CDR3 and a Joe 9 heavy chain.

Heavy and light chain clones with improved affinity over Joe 9, including clones 70-1 and 78-34, were then combined in a number of variations to determine which combination would show an improvement in affinity and/or neutralization characteristics, *e.g.*, heavy chain from clone 70-2 and light chain from clone 78-34 (see Table 2 of specification). Following characterization of the combined clones (shown as clones 101-14 through clones 26-1 in Table 2 of specification), clone 101-11 was selected for its improved k_{off} rate and its improved IC_{50} value in neutralization assays (page 119, lines 22-28, Table 2 of specification).

Clone 101-11 was selected for affinity maturation, wherein both the heavy and light chains of the antibody were used in PCR mutagenesis. Results from the analysis of clones derived from the affinity maturation of clone 101-11 are shown as clones 136-9 through 170-25 in Table 2 of specification. The resulting clones were analyzed for their ability to bind decreasing concentrations of IL-12, and for their affinity (k_{off} rate) and neutralization properties (page 119, lines 30-37 of specification).

Clone 103-14 was selected for further affinity maturation based on its improved IC_{50} value and a low k_{off} rate relative to clone 101-11. Following selection, each of the CDRs in the light chain of clone 103-14 was randomly mutagenized and used to create four libraries. The randomized libraries were screened according to the number of different selection conditions, *e.g.*, presence or absence of excess subunit p40 (IL-12 is a heterodimer comprising p40 and p35) (page 120, lines 5-19 of specification). Resulting clones from the screen are described as clones 73-B1 through 99-G11 of Table 2, and were each analyzed for their respective affinity and neutralization properties. Of the 122 antibodies which were analyzed, clone Y61 was selected for further mutation based on its improved neutralization properties (page 120, lines 20-27 and Table 2 of specification).

Selective mutagenesis was performed on antibody Y61 as described in the specification at page 121, lines 15-40 and at Table 3, wherein individual CDR positions

were chosen for mutagenesis based on whether the amino acid was in a hypermutation or a contact position. The mutagenized heavy and light chains were analyzed for their affinity and neutralization properties, wherein it was determined that antibody J695 had improved characteristics (see page 122, lines 30-35 of specification).

In sum, the specification teaches extensive screening and mutagenesis methods for identifying human antibodies with high affinity for human IL-12. The specification also teaches numerous examples of said antibodies. Applicants describe the evolution of antibody J695, beginning with antibody Joe 9 which was identified in the initial screen. Joe 9 was then mutagenized to arrive at a number of heavy and light chains which were subsequently screened for improved binding properties, thus identifying light chain 78-34 and heavy chain 70-1. Various combinations of light and heavy chains were tested, wherein clone 101-11 (comprising light chain 78-34 and heavy chain 70-1) was identified as having improved affinity properties, and was consequentially mutagenized. The resulting clones from the clone 101-11 were screened, wherein clone 103-14 was identified as having improved binding properties. Clone 103-14 was then mutagenized, wherein clone Y61 was identified following the screening of the resulting clones. Finally, Applicants teach selective mutagenesis of antibody Y61 which led to a number of antibodies with improved properties, including antibody J695. Thus, based on the above-mentioned arguments and those filed in the September 23, 2003 response, Applicants submit that the instant specification adequately describes and enables the claimed invention.

II. Rejection of Claims 2-14, 63, 74, 77-83, 87-93 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 2-14, 63, 74, 77-83, 87-93 under 35 U.S.C. 112, first paragraph, stating that the specification does not “does not reasonably convey to one skilled...that the inventor(s), at the time the application was filed, had possession of the claimed invention.” The Examiner states that the specification “only describes the structure of J695 antibody...and does not describe the structure of any other antibody that binds to IL-12 or mutant thereof.” In addition to the response filed on September 23, 2003, Applicants submit the following supplemental response.

Applicants teach the progressive technique of identifying antibodies with high affinity for IL-12 by detailing the screening and mutagenesis methods used in numerous rounds of refinement, as well as examples of antibodies identified in each round of screening. The specification teaches a method of identification, wherein an antibody with improved properties relative to the parent antibody is selected for further improvement to attain antibodies with the preferred properties, *i.e.*, a preferred dissociation constant (k_{off}). Applicants provide Table 2 of the specification (as well as Examples 1 and 2) which lists over 200 different antibody sequences and combinations thereof comprising CDR3 variable domains and the respective binding affinity data and/or neutralization data each identified and tested. For example, following the affinity maturation of clone 101-11, Applicants describe 57 clones which were identified and tested, as well as the k_{off} measurement and neutralization properties for each.

Applicants submit that the teachings of the specification include multiple species of the claimed genus, i.e. an isolated human antibody, or antigen-binding portion thereof, that binds to human IL-12 and dissociates from human IL-12 with a K_d of 1×10^{10} M or less and a k_{off} rate constant of 1×10^3 s⁻¹ or less, as determined by

surface plasmon resonance. Applicants also submit that the species taught in the specification, e.g., clone 101-11, clone Y61, are representative of the claimed invention.

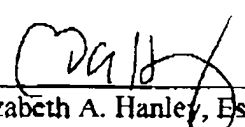
Thus, Applicants submit that one of ordinary skill in the art could follow the teachings of the specification and arrive at a fully human antibody with the same functional limitations taught by Applicants, *i.e.*, binds IL-12 with high affinity, but with different structural characteristics, *e.g.*, amino acid sequences. It is Applicants' position that the ordinarily skilled artisan can reproduce an antibody having the claimed binding characteristics, including the precise antigen-binding characteristics of the claimed antibody in view of the instant disclosure. Accordingly, applicants respectfully request that this objection to the specification and rejection of claims 2-14, 63, 74, 76-83, and 87-93 under 35 U.S.C §112, first paragraph, be reconsidered and withdrawn.

SUMMARY

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of the claims is being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. In view of the foregoing remarks, reconsideration of the rejections and allowance of all pending claims is respectfully requested. The amendments made to the claims are not related to any issues of patentability.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



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Dated: November 7, 2003